FDA Drug Safety Communication

Due to risk of serious liver injury, FDA restricts use of Ocaliva (obeticholic acid) in primary biliary cholangitis (PBC) patients with advanced cirrhosis

Adding and updating warnings

05-26-2021 FDA Drug Safety Communication

What safety concern is FDA announcing?

The U.S. Food and Drug Administration (FDA) is restricting the use of the liver disease medicine Ocaliva (obeticholic acid) in patients having primary biliary cholangitis (PBC) with advanced cirrhosis of the liver because it can cause serious harm. PBC is a rare, chronic disease affecting the ducts in the liver that carry bile, which helps with digestion. Some PBC patients with cirrhosis who took Ocaliva, especially those with evidence of advanced cirrhosis, developed liver failure, sometimes requiring liver transplant.

Based on the original clinical trials, FDA believes the benefits of Ocaliva outweigh the risks for PBC patients who do not have advanced cirrhosis. We will continue to monitor and evaluate the clinical benefit and adverse events of Ocaliva and will communicate any new information to the public if it becomes available.

What is FDA doing?

We added a new *Contraindication*, FDA's strongest warning, to the Ocaliva prescribing information and patient Medication Guide stating that Ocaliva should not be used in PBC patients with advanced cirrhosis. Advanced cirrhosis is defined as cirrhosis with current or prior evidence of liver decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia). We also revised the *Boxed Warning,* our most prominent warning, to include this information along with related warnings about this risk.

What is Ocaliva (obeticholic acid) and how can it help me?

Ocaliva was approved in May 2016 and has been shown to improve a certain liver test called alkaline phosphatase (ALP) in patients who have not responded well enough to another medicine called ursodeoxycholic acid (UDCA). The original clinical trials suggested that a decrease in ALP may improve survival and disease-related symptoms, and a clinical trial is underway to confirm this. The benefits of Ocaliva continue to outweigh the risks for adults with PBC who do not have advanced cirrhosis and have had an inadequate response to or are unable to tolerate UDCA.

What should patients and parents/caregivers do?

Patients with PBC who have cirrhosis and are taking Ocaliva should talk to your health care professional about these new warnings. Contact your prescriber immediately if you develop any of the following symptoms, which may be signs of worsening liver injury or development of advanced cirrhosis:

Any of these specific symptoms	Any of these general symptoms if they are severe or do not go away after a few days
• Swollen belly • Yellow eyes or skin • Bloody or black stools	• Belly pain • Nausea, vomiting, or diarrhea • Loss of appetite or weight loss

• Coughing up or vomiting blood • Mental status changes such as confusion, slurred speech, mood swings, changes in personality, or increased sleepiness or difficulty waking up	• New or worsening tiredness • Weakness • Fever and chills • Lightheadedness • Less frequent urination

What should health care professionals do?
Health care professionals should determine before starting Ocaliva whether a patient with PBC has advanced cirrhosis as the medicine is contraindicated in these patients. Advanced cirrhosis is defined as cirrhosis with current or prior evidence of hepatic decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia). Routinely monitor patients during Ocaliva treatment for progression of PBC with laboratory and clinical assessments to determine whether the medicine needs to be discontinued. Permanently discontinue Ocaliva in patients with cirrhosis who progress to advanced cirrhosis.

Also monitor patients for clinically significant liver-related adverse reactions that may manifest as development of acute-on-chronic liver disease with nausea, vomiting, diarrhea, jaundice, scleral icterus, and/or dark urine. Permanently discontinue Ocaliva in patients developing these symptoms.

What did FDA find?
In the five years since Ocaliva's accelerated approval, FDA identified 25 cases of serious liver injury leading to liver decompensation or liver failure associated with Ocaliva in PBC patients with cirrhosis, both in those without clinical signs of cirrhosis (compensated) or in those with clinical signs of cirrhosis (decompensated). Many of these PBC patients had advanced cirrhosis before starting Ocaliva. The 25 cases include only those submitted to FDA* and those found in the medical literature,[1] so there may be additional cases about which we are unaware (see Data Summary). All of these patients were taking Ocaliva at recommended dosages.** After starting Ocaliva, the pace of the liver decompensation or failure reported suggested these adverse events, which resulted in liver transplant in a small number of cases, were related to the drug rather than progression of the underlying PBC.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS) database from May 27, 2016, through January 18, 2021.
**We previously communicated about Ocaliva in September 2017 (risk of serious liver injury from overdosing) and February 2018 (new Boxed Warning to highlight correct dosing).

What is my risk?
All medicines have side effects even when used correctly as prescribed. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking Ocaliva. Your health care professionals know you best, so talk to them if you have questions or concerns.

How do I report side effects from Ocaliva (obeticholic acid)?
To help FDA track safety issues with Ocaliva, we urge patients and health care professionals to report side effects involving Ocaliva or other medicines to the FDA MedWatch program, using the information

in the “Contact FDA” box at the bottom of this page.

How can I sign up to receive email updates on new safety information about the medicines I am taking?
You can sign up for email alerts about Drug Safety Communications on types of drugs or medical specialties of interest to you.

Facts about Ocaliva (obeticholic acid)

- Ocaliva is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC).
- Ocaliva has been shown to improve a certain blood test that measures liver problems.
- Ocaliva is available as 5 mg and 10 mg tablets.
- Common side effects of Ocaliva include itching skin, feeling tired all over, and stomach pain or discomfort.
- In 2020, an estimated 4,300 patients filled a prescription for Ocaliva from U.S. outpatient pharmacies.[2]

Additional Information for Patients

- FDA is restricting the use of Ocaliva in patients who have primary biliary cholangitis (PBC) with advanced liver cirrhosis because the medicine can cause serious harm such as severe liver damage or liver transplant.
- Talk to your health care professional about these new warnings if you have PBC with advanced cirrhosis and are taking Ocaliva. Do not stop taking your medicine without first talking to your health care professional so they can determine if an alternative treatment may be appropriate for you.
- Read the patient Medication Guide every time you receive a prescription for Ocaliva because there may be new or important additional information about it. The Medication Guide explains the important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- To help FDA track safety issues with medicines, report side effects from Ocaliva or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines and medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is restricting the use of Ocaliva in primary biliary cholangitis (PBC) patients with advanced cirrhosis because the medicine can cause serious harm in these patients. Advanced cirrhosis is defined as cirrhosis with current or prior evidence of hepatic decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).
- Ocaliva has been found to cause liver failure in some PBC patients with advanced cirrhosis, in some cases resulting in liver transplant.
- Determine whether a patient has advanced cirrhosis before starting Ocaliva because it is contraindicated in these patients.

- Reassess patients with laboratory and clinical assessments at regular intervals while on Ocaliva treatment to monitor for progression of PBC to determine whether the medicine needs to be discontinued. Permanently discontinue Ocaliva in patients with cirrhosis who progress to advanced cirrhosis.
- Also monitor patients for clinically significant liver-related adverse reactions that may manifest as development of acute-on-chronic liver disease with nausea, vomiting, diarrhea, jaundice, scleral icterus, and/or dark urine. Permanently discontinue Ocaliva in patients developing these symptoms.
- Educate patients on the symptoms of potential liver injury or advanced cirrhosis.
- Encourage patients to read the Medication Guide they receive with their Ocaliva prescriptions because there may be new or important additional information about the medicine.
- To help FDA track safety issues with medicines, report adverse events involving Ocaliva or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines and medical specialties of interest to you.

Data Summary

FDA identified 25 cases of serious liver injury leading to liver decompensation or liver failure associated with use of Ocaliva reported in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature[1] from the drug's approval in 2016 through January 18, 2021. All of these cases described PBC patients with cirrhosis (compensated or decompensated) taking Ocaliva at recommended dosages prior to the initial liver-related adverse event.

Eighteen of 25 cases occurred in PBC patients with compensated cirrhosis who experienced liver injury that led to decompensation. Ten of these 18 patients had evidence or suspicion of portal hypertension at baseline, as suggested by one or more of the following: thrombocytopenia, varices, low albumin, and elevated bilirubin. The remaining eight cases did not provide sufficient clinical detail regarding the presence of portal hypertension. Although the disease in these PBC patients was not expected to progress rapidly, they experienced accelerated deterioration in clinical status within months of starting Ocaliva. The median time to liver decompensation (e.g., new onset ascites) after initiating Ocaliva treatment was 4 months, ranging from 2 weeks to 10 months. Four PBC patients with compensated cirrhosis required a liver transplant within 1.3 years after starting Ocaliva, and one PBC patient with compensated cirrhosis died from liver failure.

The other seven cases occurred in PBC patients with decompensated cirrhosis, two of whom died. Although there was a temporal relationship between Ocaliva initiation and liver injury, it is difficult to distinguish a drug-induced effect from disease progression in the patients with advanced baseline liver disease. The median time to a new decompensation event (e.g., hepatic encephalopathy) after initiating Ocaliva was 2.5 months, ranging from 10 days to 8 months.

In addition to liver transplant, evidence for liver decompensation included events such as new-onset ascites, variceal bleeding, hepatorenal syndrome, and worsening synthetic function. The most common associated liver-related adverse event among the 25 cases was worsening total bilirubin.

References

1. Eaton, et al. Liver injury in patients with Cholestatic liver disease treated with obeticholic acid. Hepatology 2020 Apr;71(4):1511-1514.
2. Symphony Health Metys™. Year 2020. Extracted March 2021.

Related Information

- National Institute of Diabetes and Digestive and Kidney Diseases: Primary Biliary Cholangitis (Primary Biliary Cirrhosis)
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines